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Research Article

PHARMACOKINETICS STUDY OF PUERARIN ABSORPTION IN BLOOD AFTER CONSUMPTION OF *PUERARIA TUBEROSA* WATER EXTRACT (PTWE) BY RATS

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ABSTRACT: The aim of the study was to analyse pharmacokinetics of puerarin absorption from blood *Pueraria tuberosa* tuber water extract (PTWE) and its hypoglycaemic response. Peaks of puerarin have been standardized with different types of mobile phase at 254 nm by HPLC-UV and prepared the calibration curve of puerarin. The extract was administered to the rat and their blood was collected at different time interval. The circulating PTWE in plasma was extracted with the help of acetonitryl by liquid-liquid extraction method. The extracted samples were then injected into the HPLC in order to estimate the puerarin absorption from PTWE in blood at different time interval. The concentration of blood puerarin was calculated by plotting its standard calibration curve. Further hypoglycaemic response of PTWE was also studied in diabetic rat model. The absorbed puerarin peak was found at 254 nm and its retention time (RT) is 1.6 minutes by using the mobile phase of Methanol: Ammonium acetate 10 mM buffer (60:40). After calibration, the value of C_{max} was 21.04 µg/ml, T_{max} 4 hr and total AUC as 209.04 µg hr/ml of absorbed puerarin. Through *in vivo* study, it has also been found that PTWE significantly reduces the enhanced hyperglycaemia in diabetic rats, within 8 days of treatment. The present study clearly indicated the puerarin concentration was maximum at a time interval of 4 hr and exist in rat blood plasma upto 12 hours after oral consumption of PTWE. PTWE down regulates hyperglycemia, thus act as potential anti-diabetic drug responding in short duration of time. In addition, these results provide a new approach to study the pharmacokinetic evaluation of herbal drugs (PTWE) by estimating active components (puerarin) from herbal drugs.

Key words: Puerarin, PTWE, High fat diet, Hypoglycaemic.

INTRODUCTION

Pharmacokinetic and distribution study of drug is a main step to elucidate the mechanism of drug action. Study of pharmacokinetics of herbal extract and its active constituents has always been a challenge in recent era, because herbal drug contains many phytochemicals and most of them get metabolised in the gastrointestinal tract (GIT), leading to conversion of many metabolites. High performance liquid chromatography (Yuan *et al*. 2016), liquid chromatography coupled with tandem Mass spectroscopy (LC-MS/MS), gas chromatography (Xiao *et al*. 2008) and gas chromatography mass spectrometry (Mifsud *et. al.* 2012) are the most widely used techniques to study pharmacokinetics. The classical method, high performance liquid chromatography with ultraviolet detection technique (HPLC-UV) having run times of more than 20 min (Zhong *et al*. 1996,Yamashita *et al*. 1996) was applied.

From the pharmacokinetic view, it has been found that the compounds which absorb into the blood only shows the bioactivity (Ma *et al*. 2017). The screening of each chemical constituent in herbal drug is often challenging and become a major obstacle in pharmacological investigation. Many compounds were estimated by HPLC for pharmacokinetic study such as Catechin in rabbit and rat plasma (Xie *et al*. 2011, Nakai *et al*. 2005), the active compounds found in plant *Senegelia catechu*. The pharmacokinetic evaluation of some isoflavenoidrutin and quercetin in plasma were investigated by reliable HPLC method (Ou-Yang *et al*. 2013). Some methods has

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been reported in identification and analysis of Puerarin, anisoflavonoid, found in plant Vidarikand, Hindi name Kudzu, botanical name *Pueraria tuberosa* in plasma (Maji *et al.* 2012) and fortified milk (Singh *et al*. 2013).

Pueraria tuberosa Linn. (F. Fabaceae) is an important medicinal herb utilized for the traditional system of ancient Ayurveda. According to Ayurvedic pharmacopoeia of India, the tuber of *Pueraria tuberosa* (Ayurvedic Pharmacopoeia 2006) is called Swadukanda, Ikshugandha, Kandapalash and Bhumi-kushmaand in Sanskrit. Its tubers were used since centuries as health promoting agent and considered as good rasayana (Rejuvenate). Powder of *Pueraria tuberosa* shows light green fluorescence in methanolic solution under UV 254 nm was reported in Indian Pharmacopoeia (I.P. 2010). Crude powder of *Pueraria tuberosa* was characterized by standard method (Pandey *et. al.* 2019).

According to previous works, *Pueraria tuberosa* can inhibit dipeptidyl peptidase-4 (DPP IV) enzyme activity (Srivastava *et al*. 2015). In addition to its DPP-IV inhibitory potential, it also possesses properties like anti-inflammatory (Tripathi *et al.* 2013), antioxidant (Pandey *et al.* 2007), nephroprotective (Tripathi *et al.* 2012, 2016), anti-hypertensive (Verma *et al*. 2012), anxiolytic (Pramanik *et al.* 2010) and anti- hypoglycaemic (Tripathi and Kohli 2013, Srivastava *et al*. 2015). *Pueraria tuberosa* tubers are rich in carbohydrate, alkaloids, flavonoids, tannins, steroids, triterpenoids, glycosides, protein and amino acids. Puerarin has also been studied for its antidiabetic potential in Streptozotocin in diabetogenic rat (Pandey and Tripathi 2010). The preclinical toxicity study of water extract of *Pueraria tuberosa* (PTWE) have already done as per OECD guidelines (Pandey *et al.* 2018a) and also have prepared its herbal tablet formulation (Pandey *et al.* 2018b).

Here, we have proposed the pharmacokinetic profile and drug release study with respect to its main constituent puerarin with in rat plasma. We have performed many studies on diabetes including both herbal as well as basic work (Srivastava *et al.* 2017, 2018 a,b,c, 2019 a,b,c).The previous clinical trial and animal studies have demonstrated that puerarin can improve a diabetic condition by reducing blood glucose level and (Hsu *et al*. 2003), enhancing the glucose uptake (Kato and Kawabata 2010), by protecting the pancreatic beta cells (Li *et al*. 2014) and lowering insulin resistance (Zhang *et al*. 2010). Puerarin has been found as an active constituent of PTWE, which is one of the potential hypoglycaemic-agent. In this study a simple, rapid with adequate sensitivity HPLC-UV method was developed for the determination of pharmacokinetic (plasma concentration) of puerarin. Therefore, we have also studied the hypoglycaemic activity of PTWE.

MATERIALS AND METHODS

Reagents and sample preparation Methanol and Acetonitryl as HPLC grade, buffer solutions mentioned in Table 1, Puerarin (Fig. 1) and Streptozotocin (STZ) were purchased from Sigma Aldrich. Vildagliptin and Liraglutide was gift sample provided by Novo Nordisk. *Pueraria tuberosa* (PTWE) was prepared by water decoction method. The percentage yield was at 36%.

Animal design

Rats were purchases from the central animal facility of Institute of Medical Sciences; BHU, India. Protocols were permitted by the ethical committee (Ref. no. Dean/2017/CAEC/721). The male Charles foster rats of same age group of approx. 150 gm (n=3) were used after deworming and acclimatization for 1 week. Pentobarbitone sodium (50 mg/kg) was given intra-peritonially, in order to anesthetize rats. The rats were divided into two groups, first for pharmacokinetic study and second to study the hypoglycaemic response of PTWE through fat tolerance test at 1st and 8th days of PTWE (50 mg/ 100 gbw) treatment in STZ model.

After the 5th day of STZ injection at 65 mg/kg bw, the blood glucose levels were monitored via glucometer (S.D Check) and those rats were considered diabetic whose blood glucose level was higher than 200 mg/dL. The animals were then divided into four groups. Group 1 consumes liraglutide, group 2 for vildagliptin, group 3 consumes PTWE (50 mg/100 g bw) and group 4 as diabetic control. On the first day of the experiment, they were given high fat diet HFD (12.5 ml/kg bw) (contains as a percentage of total kilo calorie; 58 % fat, 25 % protein and 17 % carbohydrate) along with the respective drugs and their blood glucose levels were checked before and after 4 hrs of HFD consumption. The drugs treatment was continued for 8 days and again the same experiment was repeated with HFD at 8th day (Fig. 6).

Pharmacokinetic Study

HPLC method was used to analyse the puerarin absorption in plasma samples by HPLC system (Agilent Technologies 1220 Infinity II LC) using column (ZORBAX 300 SB-C-18, 4.6×150 mm, 5 µm). Injection volume was standardized to 20 µl at 30^{o}C column temperature having $\ddot{e}_{max}$ at 234, 275, 320 and 254 nm. Flow rate was 1ml/min with a total run time 4 minutes.

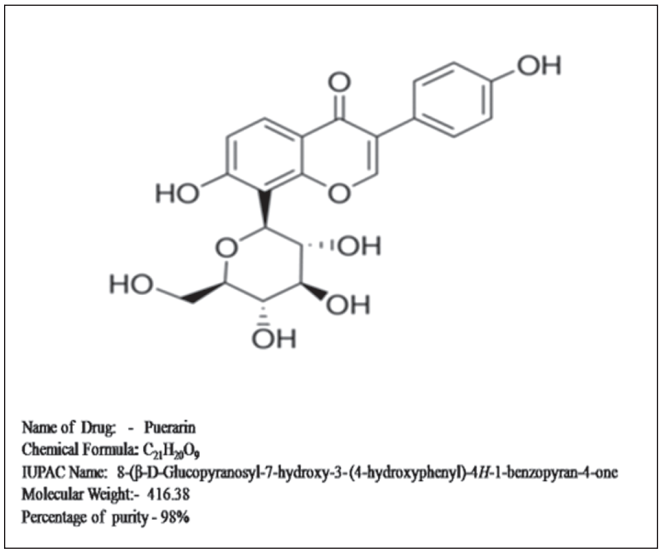

Fig. 1. Chemical Structure of Puerarin.

Estimation and standardization of retention time of puerarin by HPLC –UV

The working concentration of puerarin was prepared as 100 µg/ml. Different types of mobile phase have been used in different ratio for determination of the peaks of puerarin. Chemicals utilised to prepare mobile phase were methanol, acetonitril and buffers (ammonium acetate, potassium dihydrogen phosphate, sodium phosphate) (Table 1). The linearity of puerarin was determined by weighted least square regression analysis by plotting its standard (Fig. 3). Standard puerarin was dissolved in plasma to make different ranges of working solution. The calibration curve was shown to be linear from 60 µg/ml to 100 µg/ml. Best-fit calibration lines of chromatographic response versus concentration were determined by weighted least square regression analysis with a weighting factor of 1/concentration. Dose of PTWE up to 2000

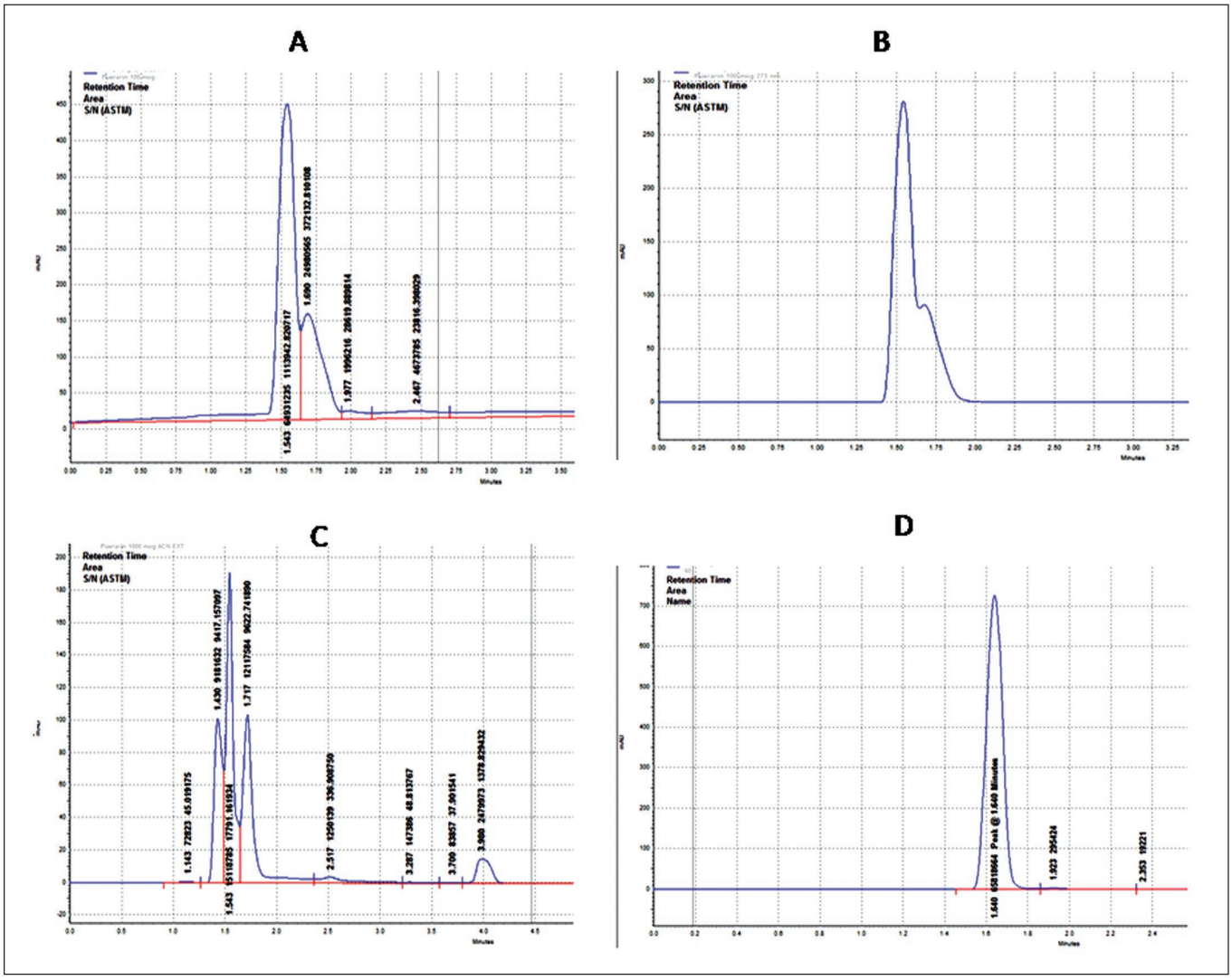

Fig. 2. HPLC Chromatogram of the peaks obtained for standard puerarin using different mobile phases.
[(A) MeOH: ACN: Buffer (0.01M KH_2PO_4) at 234 nm, (B) MeOH:Buffer (0.05 mM $NaHPO_4..2H_2O$) at 275nm, (C) ACN:Buffer (10 mM NH_4CH_3COO) at 320 nm and (D) MeOH:Buffer (0.05M KH_2PO_4) at 254 nm].

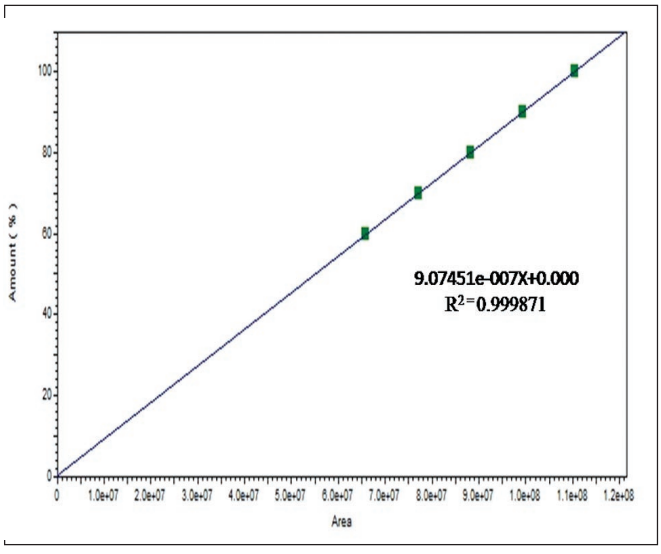

Fig. 3. Calibration curve of standard puerarin dissolved in plasma.

mg/kg bw is safe up to 7th day as a single dose, according to OECD 425, proved in our previous study (Pandey *et al*. 2018a).

Pharmacokinetic parameters of plasma samples

The blood samples were taken at the time intervals of 30, 60, 120, 240, 480 and 720 minutes and centrifuged at 4000 ± 50 rpm for 10 minutes at 2^0C to 8 ^{0}C to separate the plasma and stored in -20 ± 10^0C freezer until use. 0.25 ml of acetonitryl was added to the aliquots which was vortexed for 30 seconds before centrifugation for 10 min at 5000 rpm in order to obtain the dissolved active constituents. The supernatants were transferred in individual auto sampler vials used for injection into the HPLC. The concentration of puerarin dissolved in plasma after the PTWE consumption were determined by HPLC chromatogram and calibration line Fig. 4 and Fig.3 respectively. The value of C_{max}, T_{max} and $AUC_{(1/2\text{-}12hr)}$ of puerarin were obtained by plotting the graph between its concentration and blood isolation time (Fig. 5).

Statistical Analysis

Statistical analysis was determined by one-way ANOVA following post hoc test using Dunnetts and Tuckey by IBM SPSS Statistics Software. All results were expressed as mean ± SD. Statistical significance was considered at a p-value less than or equal to 0.05.

RESULTS AND DISCUSSION

Different type of mobile phases was used for determining the peaks of puerarin standard in rat plasma. With different mobile phase, we found 4 major good peaks at 234, 275, 320 and 254 nm, but with little tailing in first three wavelength. So, among them, the sharpest peak was found at 254 nm with RT=1.6 minutes with the use of methanol and buffer potassium dihydrogen phosphate mobile phase (60:40) in 4 minutes of HPLC running chromatogram (Fig. 2). The equation of linearity of the calibration curve of puerarin was documented in plasma with the value of Linear Fit = ax +b,9.07451e-007X+0.000 with regression R^2 = 0.999871 used to determine the concentration of drug in plasma. The linearity was plotted between 60 to 100 µg/ml. The coefficient of correlation (R^2) was consistently greater than or equal to 0.99987 during the course of standardization for puerarin. This appropriate method was validation and confirmed for estimation of puerarin (Fig. 3).

Table 1. **Different mobile phase with lambda-max and retention time.**

Mobile phase	Ratio	RT	$\lambda_{max\ (nm)}$	Peaks Findings
MeOH: ACN: Buffer (0.01 M KH_2PO_4)	30:30:40	1.5	234	Peak tailing was seen
	30:30:40	1.5	275	Peak tailing was seen
MeOH: Buffer (0.05 mM $NaHPO_4.2H_2O$)	70:30	1.5	275	Peak was found
	70:30	1.5	254	Peak was good but small deviation
	30:70	1.8	320	Peak Fronting was seen
	30:70	3.6	254	Peak fronting was seen
ACN: Buffer (10 mM NH_4CH_3COO)	20:80	3.8	254	Peak was good but small deviation
	10:90	5.5	254	Peak fronting
ACN: MeOH	50:50	5.5	275	No peak was found
MeOH: Buffer (0.05 M KH_2PO_4)	60:40	1.6	254	**Peaks was suggestive**

MeOH= Methanol, ACN= Acetonitrile

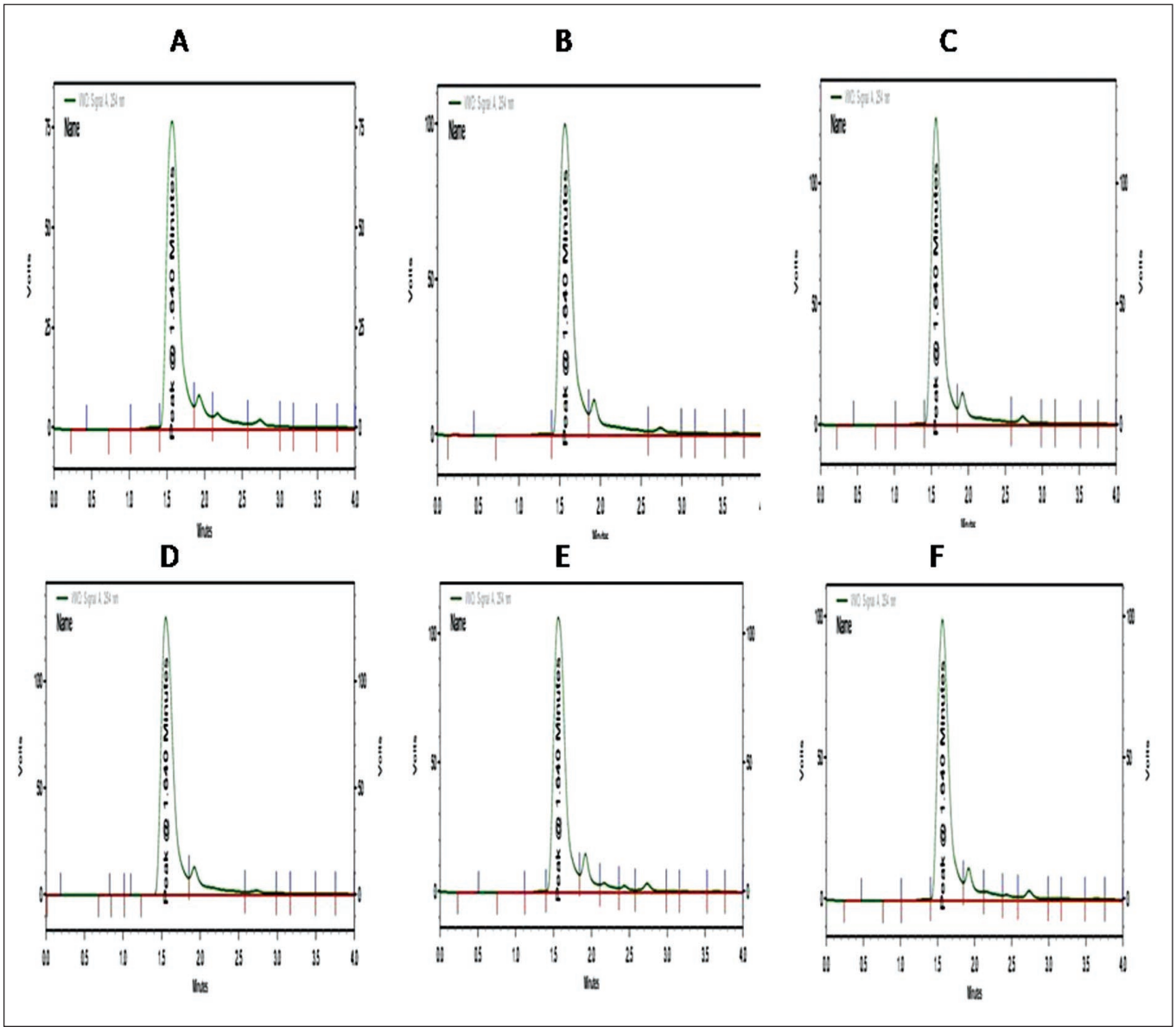

Fig. 4. HPLC chromatogram of the peaks obtained for absorbed puerarin at different time interval.
[(A) 30 min, (B) 60 min, (C) 120 min, (D) 240 min, (E) 480 min and (F) 720 min after PTWE oral consumption].

After oral administration of PTWE in rats, we have analyzed different pharmacokinetic parameters of absorbed puerarin. Peaks of absorbed puerarin in plasma were analyzed by HPLC chromatogram at different time interval (Fig. 4). The concentration of absorbed puerarin were calculated by its standard calibration curve (Fig. 3). The concentrations were observed 13.50±0.61, 16.83 ± 0.45,19.69 ± 0.81, 21.09 ± 0.86,17.14 ± 0.55 and 15.83±0.46 µg/ml at the time of 30, 60, 120, 240, 480 and 720 minutes respectively. C_{max} was found 21.09 ± 0.86 µg/ml and T_{max} was found at 240 minutes or 4 hr, the total $AUC_{(1/2\text{-}12hr)}$ was calculated as 209.04 ± 2.47 µg/ml. hr, by plotting the graph between concentration and time (Fig. 5). After comparison with diabetic control, we have found that PTWE was highly effective in inducing glucose tolerance after HFD. The cumulative dose for 8 days enhances this anti-diabetic effect. Thus, we can say that, as DPP-IV inhibitor and incretin hormones receptor agonist PTWE compresses the HFD induced hyperglycaemia. The study was focused to estimate the plasma puerarin absorption after PTWE oral consumption through pharmacokinetic (PK) study via HPLC method, also studied the hypoglycaemic activity of PTWE using diabetic rat model. The PK Study involves the quantification of drugs in the complex biological system of the body. HPLC is reliable, versatile, universal and

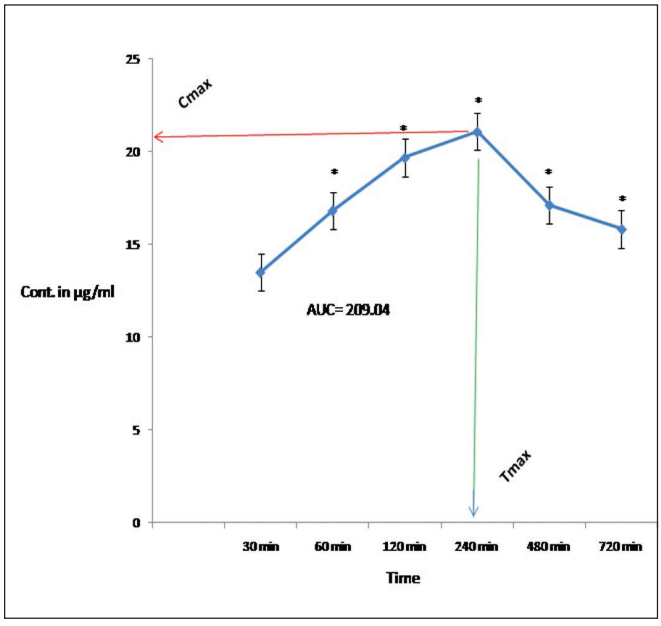

Fig. 5. The graph showing the plasma concentration of absorbed puerarin versus time of blood isolation.
[Each value represents the mean ± SD (n =3); *p < 0.05 compared with group of time 30 min].

well recognized tool for qualitative and quantitative evaluation of herbal products and their respective bioactive molecules in term of reproducibility (Pandit *et al*. 2011). Puerarin and some other constituents' content in their herbal crude extracts were earlier detected by this techniques HPLC-UV or RP-HPLC- UV (Maji *et al*. 2012, Chauhan *et al*. 2004, Singh Chauhan 2012). Here, in this work, we have estimated the concentration of puerarin absorption through PTWE in blood at different time interval.

At first, peak of puerarin has been analyzed on HPLC-UV with the use of different mobile phase (Table 1). The various mobile phases were prepared in different ratios of chemicals in order to determine the puerarin content. Finally, the mobile phase methanol and potassium dihydrogen phosphate buffer at the ratio of 60:40 was selected for further analysis. The sharp peak of puerarin was found at 254 nm without any tailing on RT 1.6 minute (Fig. 2d). Therefore, a new method was developed for estimation of puerarin absorption in plasma, which is more precise and less time consuming using methanol and potassium di-hydrogen phosphate buffer at the ratio

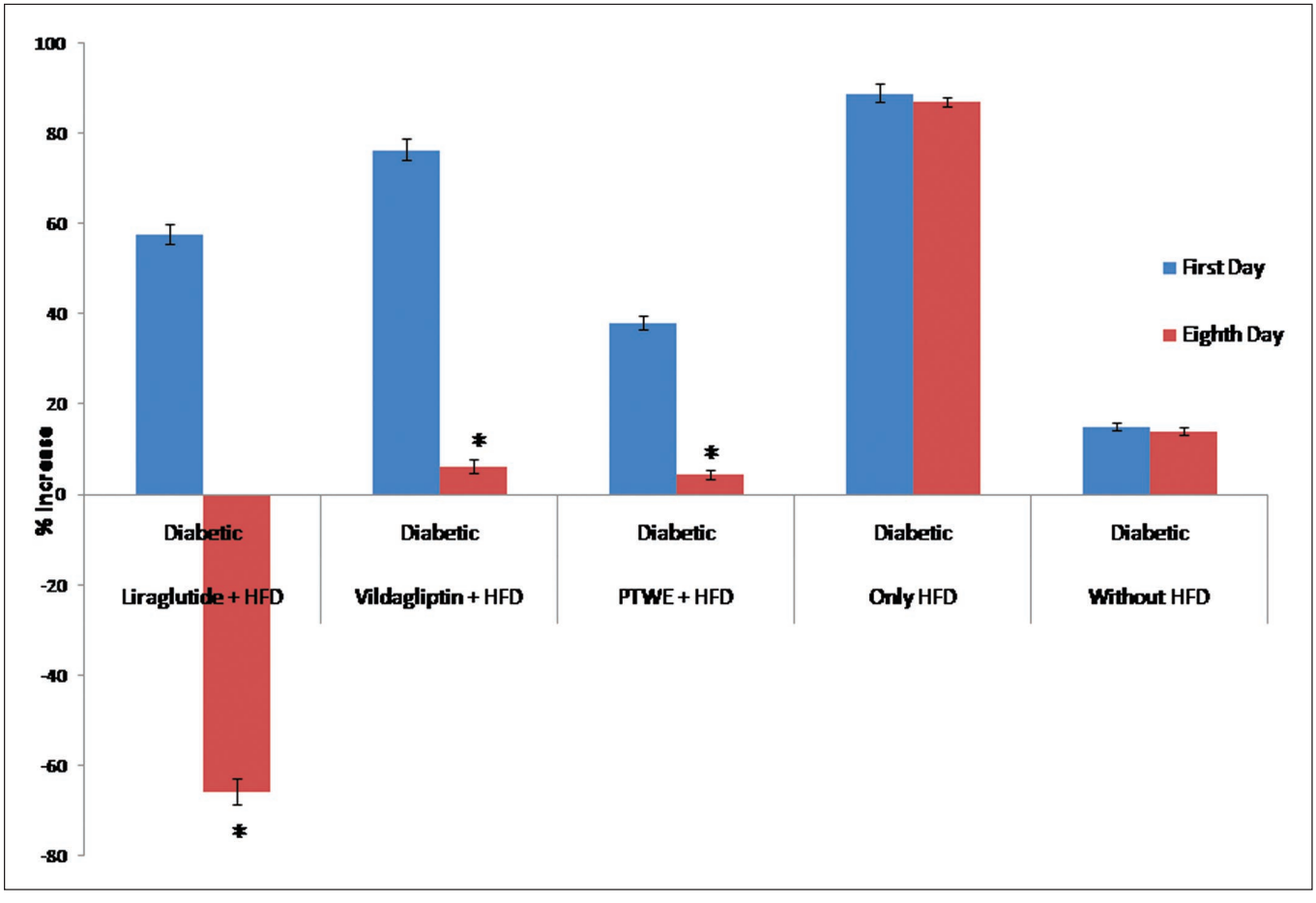

Fig. 6. Hypoglycaemic potential at 1st and 8th day of PTWE treatment against diabetic rat model.
[Each value represents the mean ± SD (n =3); *p < 0.05 compared with day 1 values].

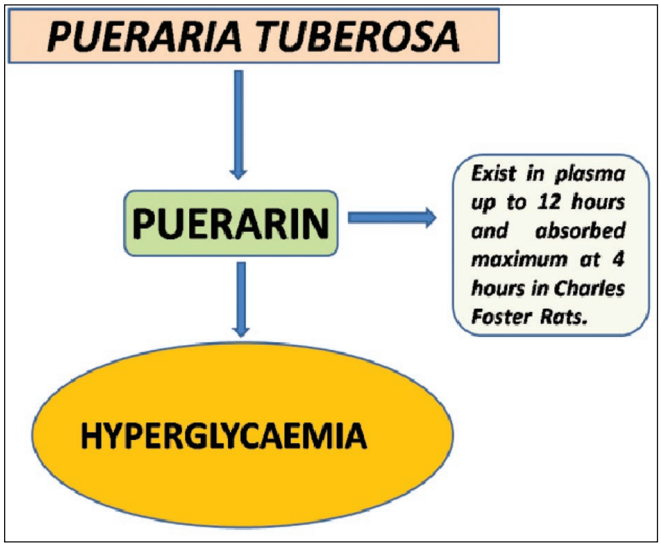

Fig. 7. Graphical abstract.

of 60:40 as mobile phase, gives the retention time (RT) 1.6 in just 4 minute of chromatogram while other previous methods (Lin *et al*. 2005) run the chromatogram for 60 minutes in order to obtain their accurate RT.

Thus, a simple analytical method was developed for determination of concentration of puerarin in plasma after PTWE consumption. This developed method is valid for linearity, reproducibility and accuracy, gives the correlation coefficient of 0.999871, indicating good linearity between absorbance and concentration (Fig. 3). In contrast to the pharmacokinetic studies which provide the information on just specific individual components (Xue *et al*. 2013, Kong *et al*. 2017, Zhao *et al*. 2014), the new method is needed in present era to estimate the active constituents from herbal crude absorption in plasma. Therefore, from obtained results, we can justify that the puerarin from PTWE absorbed maximumly to the systematic fluid in just 4 hr after oral administration.

Medicinal properties of puerarin has been studied previously for asthma (Dong *et al*. 2014), non-alcoholic fatty liver disease (NAFLD) (Zhao *et al*. 2016): endometriosis (Yu *et al*. 2015) and diabetes (Li *et al*. 2014, Asthana *et al*. 2015) etc. As puerarin is one of the main antidiabetic compositions of PTWE, we have rechecked the hypoglycaemic property of PTWE in diabetic model through high fat diet (HFD) tolerance capacity in 4 hr, both with acute and cumulative doses (Fig. 6).

The metabolism of puerarin was reported by both phase 1 and phase 2 catalytic reactions (Luo *et al*. 2012). According to these studies, the phase 2 bio-tranformation of puerarin are more important. Few enzymes are involved in the metabolism of puerarin for lucuronidation like UDP-glucuronosyltransferases 1A9 and 1A1 in human (Emi *et al*. 1995, Srinivasan *et al*. 2005). UDP-glucuronosyl transferases 1a1 and 1a7 and some others are responsible for the pharmacokinetics alteration of puerarin in Types 2 diabetic rats (He *et al*. 2014). So, these mechanisms might start from 30 min and continue up to 720 min after oral consumption of PTWE with maximum physiological function at 4 hr validated by both HPLC and in vivo study. This could be the most probable reason why this compound works rapidly and effectively against diabetes.

CONCLUSION

This detailed pharmacokinetic study provides the accurate time *i.e.*, 4 hr. at which puerarin absorbed maximum in rat's plasma after the oral consumption of PTWE and maintain the plasma concentration up to absorbed puerarin exist in plasma up to 720 min or 12 hr validating the hypoglycaemic action of PTWE in the same time duration. This information will be used to treat various diseases, discussed above where puerarin showed their medicinal properties including diabetes. Many other pharmacokinetics studies of herbal drug should be conducted in future in order to produce safer and less time-consuming property.

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